

Taurine enhances the anorexigenic effects of insulin in the hypothalamus of rats

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Abstract Taurine is known to modulate a number of metabolic parameters such as insulin secretion and action and blood cholesterol levels. Recent data have suggested that taurine can also reduce body adiposity in *C. elegans* and in rodents. Since body adiposity is mostly regulated by insulin-responsive hypothalamic neurons involved in the control of feeding and thermogenesis, we hypothesized that some of the activity of taurine in the control of body fat would be exerted through a direct action in the hypothalamus. Here, we show that the intracerebroventricular injection of an acute dose of taurine reduces food intake and locomotor activity, and activates signal transduction through the Akt/FOXO1, JAK2/STAT3 and mTOR/AMPK/ACC signaling pathways. These effects are accompanied by the modulation of expression of NPY. In addition, taurine can enhance the anorexigenic action of insulin. Thus, the aminoacid, taurine, exerts a potent anorexigenic action in the hypothalamus and enhances the effect of insulin on the control of food intake.

Keywords Obesity · Leptin · Neurotransmitter

Abbreviations

ACC Acetyl CoA carboxylase
AgRP Agouti-related peptide

Akt	Protein kinase B
AMPK	Adenosine monophosphate activated kinase
CART	Cocaine and amphetamine related transcript
FOXO1	Forkhead box protein O1
JAK2	Janus kinase 2
mTOR	Mammalian target of rapamycin
NPY	Neuropeptide Y
PAGE	Polyacrylamide gel electrophoresis
PI3K	Phosphatidylinositol 3 kinase
PMSF	Phenylmethylsulfonyl fluoride
POMC	Proopiomelanocortin
SDS	Sodium dodecyl sulphate
STAT3	Signal transducer and activator of transcription 3

Introduction

Taurine dietary supplementation is reported to exert a number of beneficial effects in diseases such as diabetes, hypercholesterolemia, ischemia and neuronal damage (Brosnan and Brosnan 2006; Lombardini and Militante 2006; Wu 2009). The mechanisms involved on its actions range from increasing insulin secretion (Ribeiro et al. 2009) and action (Carneiro et al. 2009), in diabetes; reduction of hepatic cholesterol production, in hypercholesterolemia (Murakami et al. 2010); and reduction of caspase-8 and -9, in ischemic neuronal apoptosis (Taranukhin et al. 2008). Some of these mechanisms depend, at least in part, on the antioxidant actions of taurine (Penttilä 1990; Xiao et al. 2008).

In type 2 diabetes, both experimental and clinical evidence suggest that taurine can reduce insulin resistance, leading to increased insulin-dependent glucose uptake

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(Xiao et al. 2008). In humans, it has been suggested that the taurine-dependent reduction of oxidative stress could be one of the mechanisms responsible for reducing insulin resistance, but other mechanisms have not been ruled out (Xiao et al. 2008). In experimental animals, taurine was shown to increase insulin signal transduction through the PI3-kinase pathway, resulting in increased glucose uptake (Colivicchi et al. 2004).

Besides its well known actions in peripheral tissues, insulin, acting in concert with leptin, also plays an important physiological role in the hypothalamus, controlling food intake and energy expenditure (Velloso et al. 2008). Recent studies have shown that resistance to the effects of leptin and insulin in the hypothalamus is involved in the pathogenesis of obesity and may precede peripheral insulin resistance in experimental animals with obesity and type 2 diabetes (De Souza et al. 2005; Prada et al. 2005; Milanski et al. 2009). Since taurine can improve insulin action in peripheral tissues and, bearing in mind that this amino acid is present in high amounts in the central nervous system, we decided to evaluate its effect on food intake and insulin signal transduction in the hypothalamus. Our results show that taurine can reduce food intake and stimulate all the intracellular pathways involved in insulin and leptin actions in the hypothalamus.

Materials and methods

Ethical approval

The investigation followed the University guidelines for the use of animals in experimental studies and conforms to the *Guide for the Care and Use of Laboratory Animals*, published by the US National Institutes of Health (NIH publication No. 85-23 revised 1996). The study was approved by the University of Campinas Ethical Committee. As a whole 75 rats were used in the study. Anesthesia was obtained by sodium amobarbital injection ip (15 mg kg⁻¹). For tissue extraction the rats were killed under anesthesia (thiopental 200 mg kg⁻¹).

Antibodies, chemicals and buffers

The reagents for SDS-polyacrylamide gel electrophoresis and immunoblotting were from Bio-Rad (Richmond, CA, USA). HEPES, phenylmethylsulfonyl fluoride (PMSF), aprotinin, dithiothreitol, Triton X-100, Tween 20, glycerol and bovine serum albumin (fraction V) were from Sigma (St. Luis, MO, USA). Nitrocellulose membrane (BA85, 0.2 µm) was from Amersham (Aylesbury, UK). Amobarbital and human recombinant insulin (Humulin R) were from Lilly (Indianapolis, IN, USA). Anti-JAK2 (sc-278, rabbit

polyclonal), anti-Akt (sc-1618, goat polyclonal), anti-phosphotyrosine (pY) (sc-508, mouse monoclonal), anti-phospho [Ser⁴⁷³] Akt (sc-7985-R, rabbit polyclonal), anti-STAT3 (sc-7179, rabbit polyclonal), anti-phospho [Tyr⁷⁰⁵] STAT3, anti-FOXO1 (sc-11350, rabbit polyclonal), anti-phospho [Ser²⁵⁶] FOXO1 (sc-22158-R, rabbit polyclonal), anti-AMPK (sc-25792, rabbit polyclonal), and anti-phospho [Thr¹⁷²] AMPK (sc-101630, rabbit polyclonal) antibodies were from Santa Cruz Biotechnology (Santa Cruz, CA, USA). Anti-phospho [Ser⁷⁹] acetyl CoA carboxylase (ACC) (#07-184, rabbit polyclonal) antibody was from Upstate Biotechnology (Charlottesville, VA, USA). Anti-mTor (#4517, mouse monoclonal) and anti-phospho [Ser2448] mTor (#2971, rabbit polyclonal) antibodies were from Cell Signaling (Danvers, MA, USA). Anti β-actin (#ab6276, mouse monoclonal) was from Abcam (Cambridge, MA, USA). The PI3 K inhibitor LY294002, the JAK2 inhibitor AG490 and the AMPK activator, AICAR, were from EMD Chemicals (Darmstadt, Germany).

Determination of blood glucose and insulin levels

Glucose was determined in blood using a glucometer from Abbott (Opptimum, Abbott Diabetes Care, Inc., Alameda CA, USA). Insulin was determined in serum using an ELISA kit (sensitivity 0.2 ng/ml) from Millipore (Billerica, MA, USA).

Animal model and experimental protocols

In all experiments, 8-week-old male Wistar rats with a body weight of 250–300 g were employed. The animals were maintained on a 12:12 h artificial light–dark cycle and housed in individual cages. The animals were stereotactically instrumented to receive a cannula placed in the lateral ventricle, as previously described (Paxinos et al. 1980). After 7 days, the correct location of the cannula was tested by injecting 2.0 µl (10⁻⁶ M) angiotensin II (0.002 nmol) and determining the thirst response (Milanski et al. 2009). For this, rats were water deprived for 2 h and immediately after i.c.v. injection of angiotensin II, a bottle containing 10.0 ml water was made available. Only the rats spontaneously drinking at least 5.0 ml water in 30 min were considered correctly cannulated and used in the experiments. For evaluation of spontaneous food intake, the rats were food deprived for 6 h (12:00–6:00 PM) and then treated with a single dose (2.0 µl) of insulin (1.0 µM; 0.002 nmol), taurine (1.0, 3.0 or 5.0 mM; 2.0, 6.0 or 10.0 nmol), or insulin (1.0 µM; 0.002 nmol) + taurine (3.0 mM; 6.0 nmol). Food intake was determined after 2 and 12 h. For immunoblot experiments, i.c.v. cannulated rats were acutely treated with a single dose (2.0 µl) of insulin (1.0 µM; 0.002 nmol), taurine (3.0 mM; 6.0 nmol)

or insulin (1.0 μ M; 0.002 nmol) + taurine (3.0 mM; 6.0 nmol) and the hypothalami were obtained for protein extract preparation. In some experiments, rats were treated in advance with a single dose of LY294002 (3.0 pmol), AG490 (10.0 pmol) or AICAR (25.0 mM).

Evaluation of spontaneous locomotor activity

I.c.v. cannulated rats were acutely treated with a single dose (2.0 μ l) of insulin (1.0 μ M; 0.002 nmol), taurine (3.0 mM; 6.0 nmol) or insulin (1.0 μ M; 0.002 nmol) + taurine (3.0 mM; 6.0 nmol) and spontaneous locomotor activity was evaluated over 30 and 90 min periods using a computer-controlled detection system from Harvard Instruments (Panlab, Holliston, MA, USA).

Immunoprecipitation and immunoblotting

For evaluation of protein expression and activation of signal transduction pathways, the hypothalami of anesthetized rats were excised and immediately homogenized in solubilization buffer at 4°C [1% Triton X-100, 100 mM Tris-HCl (pH 7.4), 100 mM sodium pyrophosphate, 100 mM sodium fluoride, 10 mM EDTA, 10 mM sodium orthovanadate, 2.0 mM PMSF and 0.1 mg aprotinin/ml] with a Polytron PTA 20S generator (model PT 10/35; Brinkmann Instruments, Westbury, NY, USA). Insoluble material was removed by centrifugation for 40 min at 11,000 rpm in a 70.Ti rotor (Beckman) at 4°C. The protein concentration of the supernatants was determined by the Bradford dye method. Aliquots of the resulting supernatants containing 0.02–0.1 mg of protein extracts were separated by SDS-PAGE, transferred to nitrocellulose membranes and blotted with antibodies. Specific bands were detected by chemiluminescence and capture was performed with a Syngene GBox (Imgen Technologies, Alexandria, VA, USA).

Real-time PCR

The expressions of NPY and POMC mRNAs were measured in hypothalami obtained from rats treated icv with insulin (2.0 μ L, 1.0 μ M; 0.002 nmol) or taurine (2.0 μ L, 3.0 mM; 6.0 nmol). Intron-skipping primers were obtained from Applied Biosystems (Rn00561681_m1 and Rn00595020_m1, for NPY and POMC, respectively). Glyceraldehyde-3-phosphate dehydrogenase primers were used as a control. Real-time PCR analysis of gene expression was performed with an ABI Prism 7700 sequence detection system (Applied Biosystems). The optimal concentration of cDNA and primers, as well as the maximum efficiency of amplification, were obtained through five-point, two-fold dilution curve analysis for each gene. Each PCR contained 3.0 ng of reverse-transcribed RNA, 200 nM of each specific

primer, TaqManTM (Applied Biosystems), and RNase free water in a final volume of 20 μ l. Real-time data were analyzed using the Sequence Detector System 1.7 (Applied Biosystems) (Bertelli et al. 2006).

Statistical analysis

Specific protein bands present in the blots were quantified by digital densitometry (Dimension, Imgen Technologies, Alexandria, VA, USA). Mean values \pm SEM obtained from densitometry scans, real-time PCR, metabolic measurements and spontaneous activity were compared using one-way ANOVA followed by Tukey–Kramer post-hoc test; $p < 0.05$ was accepted as statistically significant.

Results

Taurine injection in the hypothalamus reduces food intake and spontaneous activity

The acute injection of a single dose of taurine i.c.v. in the hypothalamus produces a dose-dependent reduction of spontaneous food intake (Fig. 1a). This effect is of similar magnitude to that produced by insulin, reducing food intake by approximately 30% over a period of 3 and 12 h (Fig. 1b). Moreover, taurine and insulin have additive effects as simultaneous injections of both compounds produce a net food intake reduction that is 15% lower than that achieved by either compound alone (Fig. 1b). In addition, taurine, but not insulin, promoted a reduction of spontaneous activity measured over a period of 90, but not 30 min (Fig. 1c).

Taurine modulates signal transduction through the same pathways targeted by insulin

The injection of a single i.c.v. dose of taurine in the hypothalamus activates signal transduction through the Akt/FOXO1 (Fig. 2a, b), JAK2/STAT3 (Fig. 2c, d) and mTOR/AMPK/ACC (Fig. 2e–g) pathways. Interestingly, in at least four of the evaluated proteins, taurine significantly increases the effect of insulin: FOXO1 (Fig. 2b); JAK2 (Fig. 2c); STAT3 (Fig. 2d); and, mTOR (Fig. 2e). All the effects of taurine on hypothalamic signal transduction occurred independently of any change in blood glucose and insulin levels (Fig. 3a, b).

Taurine reduces NPY expression in the hypothalamus

Since the anorexigenic action of insulin in the hypothalamus depends on neurotransmitter expression, we evaluated

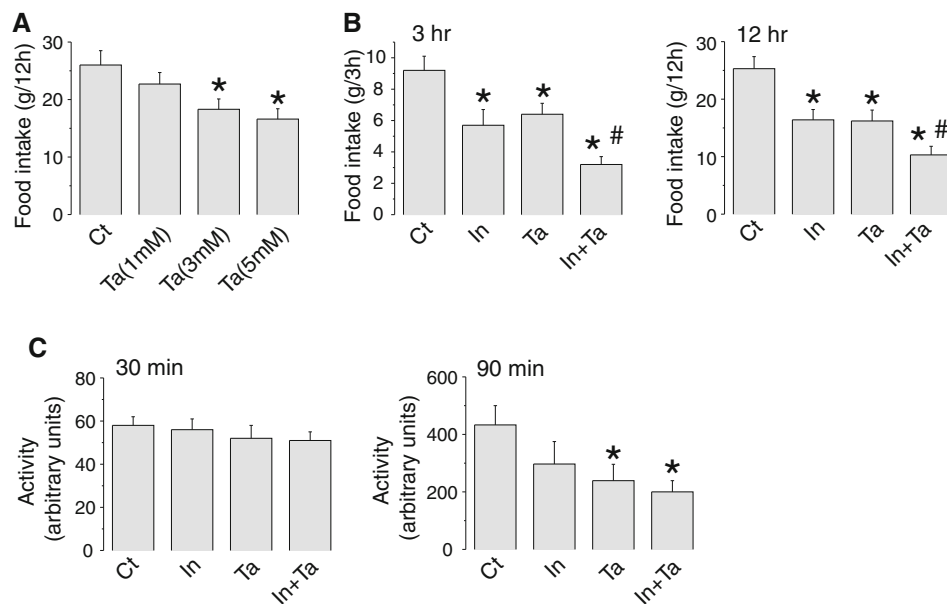


Fig. 1 Taurine inhibits food intake and spontaneous activity. I.c.v. cannulated rats were food deprived for 6 h and treated with saline (2.0 μ L) (Ct) or taurine (2.0 μ L, 1.0, 3.0 or 5.0 mM) (Ta) just before food reintroduction for determination of spontaneous food intake over 12 h (**a**); another group of rats were treated with saline (2.0 μ L) (Ct), insulin (2.0 μ L, 10^{-6} M) (In), taurine (2.0 μ L, 3.0 mM) (Ta), or a combination of insulin and taurine (2.0 μ L, 10^{-6} M and 2.0 μ L,

3.0 mM, respectively) (In + Ta) and spontaneous food intake was determined over 3 and 12 h (**b**, *left-*, and *right-hand panels*, respectively). In another group of rats treated similarly to that described in **b**, spontaneous activity was measured over 30 and 90 min (**c**, *left-*, and *right-hand panels*, respectively). In all experiments, $n = 5$, * < 0.05 vs. Ct; # < 0.05 vs. In

the effects of taurine in two neurotransmitters expressed by first order hypothalamic neurons. Similarly to insulin, taurine alone is capable of reducing the hypothalamic expression of NPY (Fig. 4a) without affecting the expression of POMC (Fig. 4b).

The anorexigenic effect of taurine is targeted by inhibitors of the PI3 K and JAK2

To define the main pathways involved in taurine-induced reduction of feeding, we employed chemical inhibitors of PI3 K and JAK2 and an inducer of AMPK activity, in parallel with i.c.v. taurine. As depicted in Fig. 4, the inhibition of either PI3 K (Fig. 5a) or JAK2 (Fig. 5b) completely blocks the anorexigenic effect of taurine. Conversely, treatment with the AMPK stimulating compound, AICAR, promotes only a partial reversion of the anorexigenic effect of taurine (Fig. 5c).

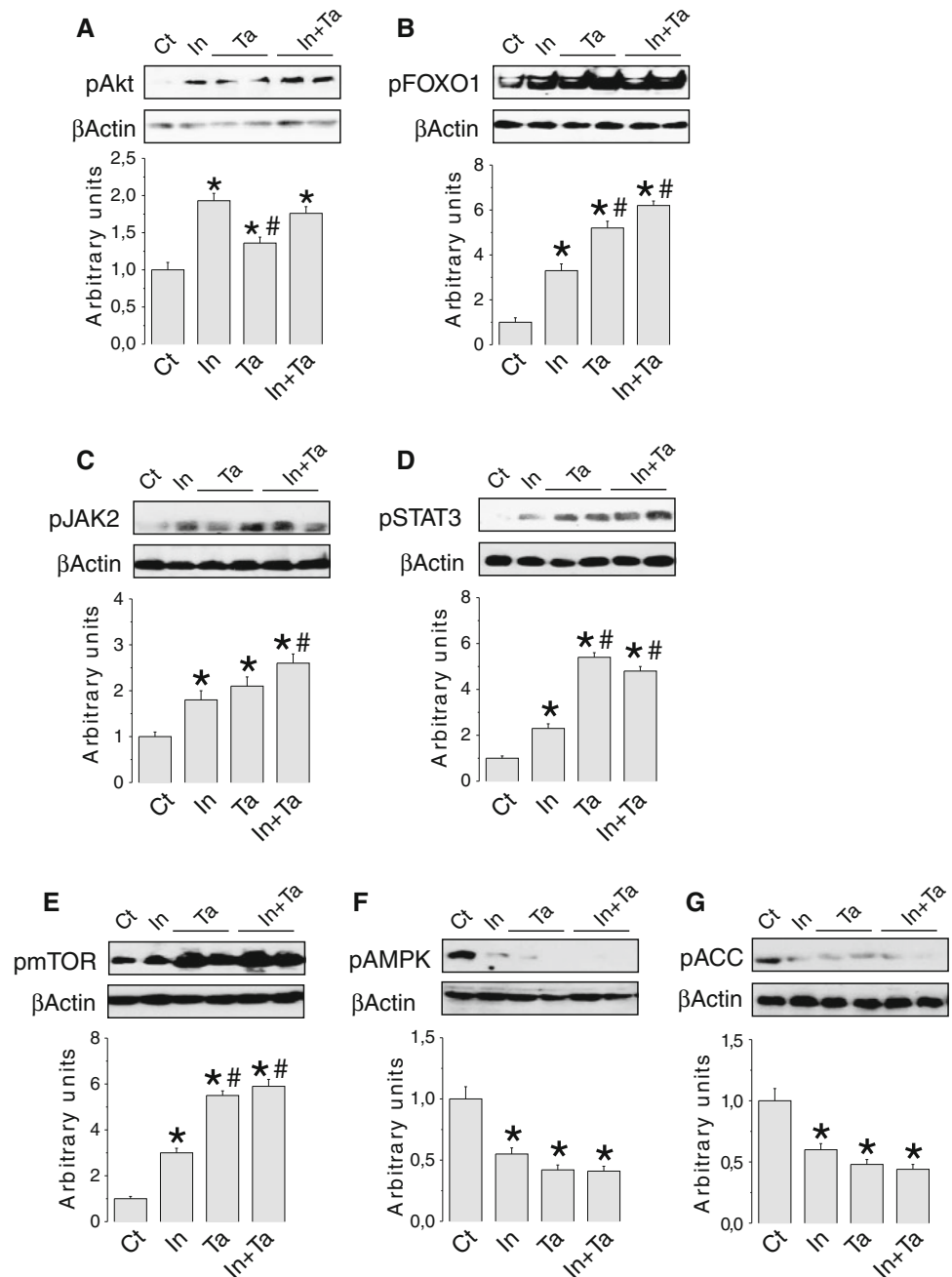
Discussion

Following the identification of leptin in 1994 (Zhang et al. 1994), great progress has been obtained in the characterization of the roles played by the hypothalamus in the control of feeding, thermogenesis and adiposity. Leptin and insulin provide the most robust adiposity signals acting

primarily, but not exclusively, through first-order neurons of the arcuate nucleus (Araujo et al. 2010). In addition, a number of hormones and nutrients provide satiety signals that play important roles in the initiation and termination of a meal (Murphy and Bloom 2006; Moran 2009; Blevins and Baskin 2010). The hypothalamic signals generated by some of these hormones and nutrients can integrate with the adipostatic signals produced by leptin and insulin, therefore modulating the energy balance in the whole body (Murphy and Bloom 2006; Blevins and Baskin 2010). At the molecular level, this integration of signals occurs through conserved pathways, where the JAK2/STAT3, PI3 K/Akt/FOXO1 and AMPK/ACC pathways are the most relevant (Murphy and Bloom 2006; Araujo et al. 2010). Some examples of molecular cross-talk in the hypothalamus, which lead to the modulation of energy homeostasis, have been recently explored and invariably involve one or more of the pathways described above. Thus, adiponectin, an adipokine produced in the adipose tissue, can enhance the hypothalamic actions of insulin by activating the IRS/PI3 K/Akt pathway (Coope et al. 2008), while leucine can modulate insulin/leptin signaling through the AMPK pathway (Ropelle et al. 2008).

Despite the rapid progress in the characterization of the involvement of the hypothalamus in the genesis of obesity, no major innovation has been introduced so far in the treatment of this prevalent disease. Most efforts to limit or

Fig. 2 Taurine activates signal transduction in the hypothalamus. I.c.v. cannulated rats were treated with saline (2.0 μ L) (Ct), insulin (2.0 μ L, 10^{-6} M) (In), taurine (2.0 μ L, 3.0 mM) (Ta), or a combination of insulin and taurine (2.0 μ L, 10^{-6} M and 2.0 μ L, 3.0 mM, respectively) (In + Ta) and, after 10 min, hypothalami were obtained for total protein extract preparation for SDS-PAGE and immunoblotting for detection of phosphorylated (p) forms of Akt (a), FOXO1 (b), JAK2 (c), STAT3 (d), mTOR (e), AMPK (f) and ACC (g). All membranes were stripped and reblotted with anti- β -actin antibodies. In all experiments, $n = 7$, * < 0.05 versus Ct; # < 0.05 versus In



reduce body adiposity still rely on behavioral approaches and on the employment of a few drugs that produce a body weight reduction of 10–15%, at most. Thus, characterizing novel mechanisms involved in the control of feeding and thermogenesis may uncover potential targets for the development of more efficient methods to tackle this disease.

In association with a number of studies advocating a beneficial role for taurine in diabetes, atherosclerosis and neural ischemia, recent studies have reported the potential role for taurine in obesity. Initially, it was suggested that the nutritional deficiency of taurine could predispose to

obesity (Tsuboyama-Kasaoka et al. 2006). This was followed by the demonstration of a reduced adiposity in *C. elegans* cultivated in a taurine rich medium (Kim et al. 2010). Finally, a recent study showed a reduction of body adiposity in a rodent model of obesity treated with taurine supplementation (Nardelli et al. 2010). Therefore, we decided to evaluate the hypothalamic effects of taurine on the modulation of feeding.

Initially, we showed that taurine exerts a potent and dose dependent anorexigenic effect when injected in the hypothalamus. This effect is of similar magnitude to the effect produced by either insulin or leptin (Coope et al. 2008),

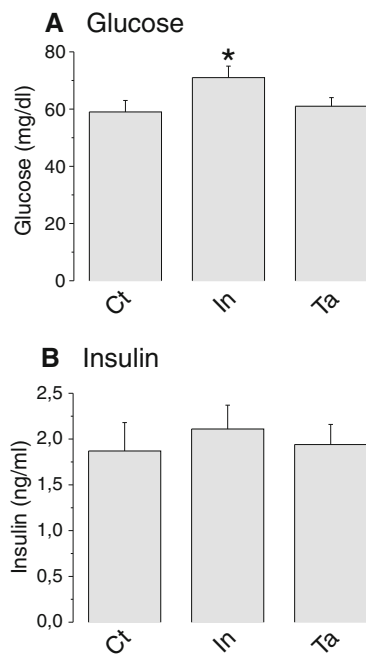


Fig. 3 Taurine exerts no effect on systemic levels of glucose and insulin. I.c.v. cannulated rats were treated with saline (2.0 μ L) (Ct), insulin (2.0 μ L, 10^{-6} M) (In) or taurine (2.0 μ L, 3.0 mM) (Ta) and, after 3 h, blood samples were collected for determination of glucose (a) and insulin (b) levels. In all experiments, $n = 7$, * < 0.05 versus Ct

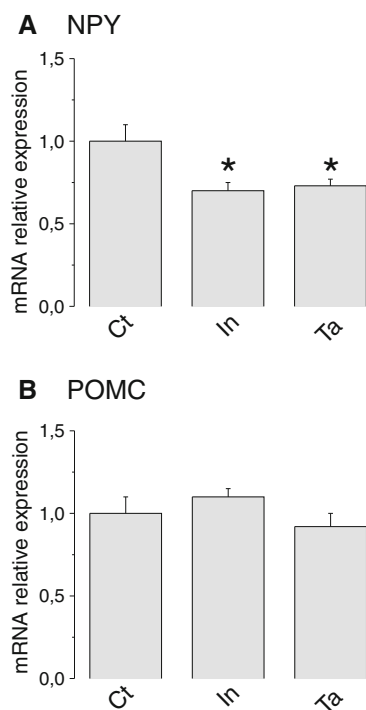


Fig. 4 Taurine modulates NPY expression in the hypothalamus. I.c.v. cannulated rats were treated with saline (2.0 μ L) (Ct), insulin (2.0 μ L, 10^{-6} M) (In) or taurine (2.0 μ L, 3.0 mM) (Ta) and, after 3 h, hypothalami were obtained for RNA preparation for real-time PCR for NPY (a) and POMC (b). In all experiments, $n = 5$, * < 0.05 vs. Ct

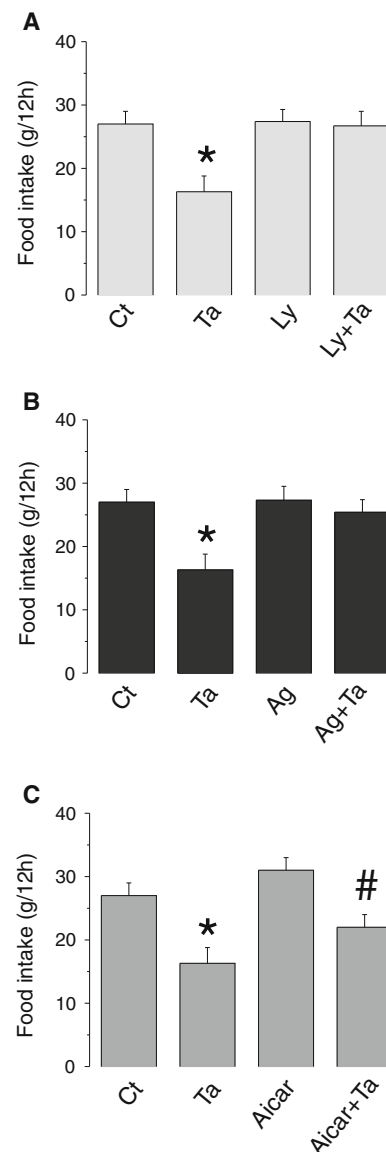


Fig. 5 Exploring the pathways involved in taurine action in the hypothalamus. I.c.v. cannulated rats were food deprived for 6 h and treated with saline (2.0 μ L), LY294002 (2.0 μ L, 3.0 pmol) (a), AG490 (2.0 μ L, 10.0 pmol) (b) or AICAR (2.0 μ L, 25.0 mM) (c), right after the animals were treated with saline (2.0 μ L) (Ct) or taurine (2.0 μ L, 3.0 mM) (Ta) just before food reintroduction for determination of spontaneous food intake over 12 h. In all experiments, $n = 7$, * < 0.05 versus Ct; # < 0.05 versus Ta

alone. In addition, when administered simultaneously with insulin, an enhancement of the anorexigenic actions of either compound alone was obtained. Thus, the potential for taurine to act as an insulin-sensitizing compound goes beyond its effects on peripheral tissues, as previously reported (Wu et al. 2010). Interestingly taurine also produced an inhibitory effect on the spontaneous activity of rats. Although this may have an impact on food intake, since reducing locomotion may reduce the search for food, another possibility is that the increased primary satiety

produced by taurine may result on lower activity. Further studies will be required to clarify this issue.

To define the molecular mechanisms involved in the anorexigenic effect of taurine, we evaluated proteins involved in the orexigenic/anorexigenic signaling of three distinct pathways. In all cases, taurine acted similarly to insulin, stimulating the activities of the Akt/FOXO1 and JAK2/STAT3 signaling pathways, while inhibiting the AMPK signaling pathway. In four of the evaluated proteins, taurine was capable of enhancing the effect of insulin alone, in accordance with the effect of taurine on the suppression of food intake. Importantly, no changes in the systemic levels of either glucose or insulin were produced by the i.c.v. treatment with taurine, excluding an indirect mechanism, acting through endogenous insulin, in the effects herein reported.

Most of the hypothalamic actions of insulin are mediated by first-order neurons of the arcuate nucleus (Araujo et al. 2010; Blevins and Baskin 2010). Two distinct subpopulations of neurons coexist in this anatomical region. Orexigenic neurons expressing NPY and AgRP, which are mostly active during fasting, and anorexigenic neurons expressing POMC and CART, which are active following a meal (Araujo et al. 2010; Blevins and Baskin 2010). The expressions of such neuropeptides are rapidly modulated following an anorexigenic stimulus and correlate very well with the respective mRNA levels (Pittius et al. 1985; Schwartz et al. 1992). Previous studies have shown that insulin alone can reduce NPY expression, whereas only leptin or a combination of leptin and insulin can increase the expression of POMC. Here, taurine was capable of reproducing the effects of insulin, reducing the expression of NPY, without affecting the expression of POMC (Araujo et al. 2010; Blevins and Baskin 2010).

In the last part of the study, we used a pharmacological approach to define the impact of each of the analyzed signaling pathways, i.e., PI3 K/Akt/FOXO1, JAK2/STAT3 and AMPK, on the anorexigenic actions of taurine. Interestingly, the inhibition of either PI3 K or JAK2 resulted in the complete abolition of the effect of taurine. However, while the treatment with the AMPK stimulating agent, AICAR, increased basal food intake, its effect on taurine suppression of feeding was only partial. Since the PI3 K and JAK2 signaling pathways have rather overlapping and complementary roles in the control of feeding, we suspect that by inhibiting either of these pathways we almost completely disrupted the action of taurine. Conversely, although the AMPK pathway can establish a cross-talk with either the PI3 K and/or the JAK2 signaling systems, it plays a minor role in the net effect of taurine, as it occurs with insulin (Ropelle et al. 2008).

In summary, the aminoacid, taurine, acts in the hypothalamus to suppress food intake and enhance the action of

one of the most important adipostatic messengers, insulin. These data reinforce the clinical and nutritional observations regarding an anti-adipogenic action of taurine, providing a mechanistic basis for this effect. Although we have shown the capacity of taurine to act in the hypothalamus through the insulin signaling pathway, the mechanism by which the taurine signal is generated remains unknown.

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